STIC-ILL

VO 5/5

From: Li, Janice
Sent: Monday, May 05, 2003 3:02 PM
To: STIC-ILL
Subject: 10023335

444137

Please provide the following:

TI Ethopharmacology of imipramine in the forced-swimming test: gender differences
AU Barros H M T (Reprint); Ferigolo M
SO NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS, (DEC 1998) Vol. 23, No. 2, pp. 279-286.

TI Strain Differences in the Behavioral Effects of Antidepressant Drugs in the Rat Forced Swimming Test
AU Lopez-Rubalcava, C.; Lucki, I.
SO Neuropsychopharmacology (1999), Volume Date 2000, 22(2), 191-199.

TI Open field, learned helplessness, conditioned defensive burying, and forced-swim tests in WKY rats.
AU Pare W P
SO PHYSIOLOGY AND BEHAVIOR, (1994 Mar) 55 (3) 433-9.

10466161

TI Differences in the stress response of Wistar-Kyoto (WKY) rats from different vendors.
AU Pare W P; Kluczynski J
CS V. A. Medical Center, Perry Point, MD 21902-1040, USA.. wpare@aol.com
SO PHYSIOLOGY AND BEHAVIOR, (1997 Sep) 62 (3) 643-8.

TI Behavioural profiles of two Wistar rat lines selectively bred for high or low anxiety-related behaviour
AU Liebsch G; Montkowski A; Holsboer F; Landgraf R (Reprint)
SO BEHAVIOURAL BRAIN RESEARCH, (AUG 1998) Vol. 94, No. 2, pp. 301-310.

TI A biobehavioral profile of an ulcer susceptible rat strain
AU Pare, William P.; Redei, Eva
CS Eastern Research and Development Office, VA Medical Center, Perry Point, MD, 21902, USA
SO Hans Selye Symposia on Neuroendocrinology and Stress (1995), 2(Neuroendocrinology of Gastrointestinal Ulceration), 201-8

9505559

TI Characterization of Wistar Kyoto (WKY) rat sub-strains selectively bred for depressive-like behavior in the forced swim test.
AU Solberg, L. C. (1); Will, C.; Turek, F. W. (1); Redei, E.
SO Society for Neuroscience Abstracts., (1999) Vol. 25, No. 1-2, pp. 849.
Meeting Info.: 29th Annual Meeting of the Society for Neuroscience. Miami Beach, Florida, USA October 23-28, 1999 Society for Neuroscience

Q. Janice Li, M.D.
Patent Examiner, AU1632
CM1, Rm11A17
Mail Box 12E12
703-308-7942

A BIOBEHAVIORAL PROFILE OF AN ULCER SUSCEPTIBLE RAT STRAIN

William P. Paré, and Eva Redei

Selye[1,2] not only formalized the stress concept, but made stress the legitimate subject of scientific inquiry. Since his seminal publications, we recognize that stress is a ubiquitous phenomenon that is related to the development of many diseases,[3,4] including mood disorders[5]. Everyone is exposed to stress in one form or another, but not all individuals succumb to the effects of stress. It is also intriguing that, in some cases, a seemingly innocuous stressor can cause profound disturbances in some subjects, but have little effect on others. This problem of subject variability is countered by examining the effects of stress in an individual that is either hyperreactive to stress, or is either predisposed to the illness under study. Therefore stress hyperreactive animal strains are valuable tools in studying the connections between disease states and stress. We have observed that the Wistar Kyoto (WKY) rat strain is vulnerable to stress effects.

The WKY rat strain was developed as the normotensive control strain to the spontaneously hypertensive rat (SHR)[6]. While the WKY rat may be an appropriate control strain for hypertension studies, the strain manifests certain behavioral idiosyncrasies and cannot be considered a normal control strain for behavioral studies[7]. Our investigations have indicated that WKY rats manifest distinct behavioral and physiological responses to stress. These responses suggest the presence of a biobehavioral profile in WKY rats with stress ulcer susceptibility and behavioral depression as major manifestations of this profile.

BEHAVIORAL STUDIES

When WKY rats are observed in the open field test of emotionality, they exhibit little exploratory behavior. WKY rats rapidly adopt an immobile posture in the Porsolt forced swim test. In addition, WKY rats readily acquire a learned helplessness response[8]. The forced swim test and the learned helplessness procedure are putative models of depression[9]. WKY rats score highly in both procedures. Therefore, we have suggested that WKY rats are prone to depressive behavior[10].

While WKY rats typically obtain high score on behavioral tests of depressive behavior, the question remains whether other tests of emotional behavior will also

Neuroendocrinology of Gastrointestinal Ulceration
Edited by S. Szabo and Y. Taché, Plenum Press, New York, 1995

discriminate between WKY rats and rats from other strains. To address this question, WKY, Wistar and Fischer-344 (F-344) rats were exposed to one of three behavioral test of anxiety[11]. Thus, rats from all three strains were exposed to either the defensive-withdrawal test[12], the elevated plus maze[13], or the defensive burying test[14]. Anxiolytic agents typically influence behaviors in these three tests. Following behavioral testing, all rats were then exposed to the ulcerogenic water-restraint procedure[15]. None of these tests were consistently effective in discriminating WKY rats from the other two strains, except the defensive burying test. The response, however, of WKY rats in the defensive burying test was unorthodox. The "anxiety" response in defensive burying involves burying, with bedding material, a shocking prod that protrudes from one of the test enclosure walls. Rats from the other strains invariably showed this burying response after being shocked by the prod, but WKY rats consistently withdrew to the opposite corner of the cage and remained immobile throughout the testing period. We believe that this immobility response is just another manifestation of depressive behavior in WKY rats. In addition, WKY rats in this study had more ulcer when subsequently exposed to restraint stress[11].

WKY rats also perform consistently on different tests of depressive behavior. WKY and Wistar rats were exposed, in a semi-random fashion, to the open field test, the defensive burying test, the Porsolt forced swim test, and the learned helplessness paradigm. The forced swim test was positively correlated with the learned helplessness procedure and, to a lesser degree with defensive burying, but these relationships were observed only in WKY rats, not Wistar rats. We concluded that WKY rats represented a more sensitive strain for detecting possible relationships between putative animal models of depression. Following the conclusion of the behavioral testing, all rats were exposed to water-restraint stress. WKY rats also had more ulcers than Wistar rats[16].

If the predominant coping strategy for WKY rats is freezing and immobility, then WKY rats should be superior in adopting a passive avoidance response, wherein the learned response involves the inhibition of a prepotent active response. We observed this to be the case when WKY, Wistar and F-344 rats were tested in two passive avoidance procedures - a platform step-down procedure and a light chamber - dark chamber one-way avoidance procedure. Rats were assigned to either one of the two procedures and then exposed to water-restraint stress. WKY rats not only adopted these passive avoidance responses faster that Wistar and F-344 rats, but demonstrated a fascinating behavior in the one-way avoidance task. While rats from the other strains would re-enter, during extinction trials, the dark compartment in which shock had been previously experienced, WKY rats would straddle the threshold between the two chambers for the duration of the testing period. We have labelled this behavior, "ambivalence behavior," and propose that it reflects the decision-making paralysis that characterizes depressed patients. WKY rats also had more ulcer following water-restraint stress[17].

The propensity to recall unpleasant memories contributes to the symptomatology of depression[18]. This phenomenon was observed in WKY rats. WKY and Wistar rats were trained on a one-way avoidance task (i.e., the unpleasant event) but were also exposed to grid shock, either prior to (i.e., the proactive treatment) or after (i.e., the retroactive treatment) passive avoidance training. Subsequent test trials revealed that the retention of the unpleasant event was more pronounced for the proactive treatment, and this effect was dramatically greater in WKY rats as compared to Wistar rats.

There are many other symptoms that characterize depression. Reduced appetite and loss of body weight are symptoms of depression[19]. When hungry WKY, Wistar and F-344 rats are provided with the opportunity to acquire a food pellet in the middle of a novel open field, the number of feeding contacts is significantly less in WKY rats as compared to other rats. This fear of feeding in a novel environment, or "hyponcophagia," is significantly greater in WKY rats[20]. Loss of appetite, or decreased feeding following exposure to stress, is frequently been reported as a measure of response to stress[21,22], but the capacity of a novel environment to produce a strain-specific anhedonic response has never been reported.

The prevalence of the female gender in mood disorders[23,24] is also reflected in WKY rats. Previous research on the question of differential sex susceptibility to stress effects had produced conflicting results. But our studies revealed that proestrus-estrus female WKY rats were judged as more depressed, according to the Porsolt forced swim test, as compared to WKY female diestrus rats and WKY male rats. In addition, proestrus-estrus WKY female rats developed more ulcers when exposed to water-restraint stress[25]. These data imply that reactivity to stress may be influenced, not only by the animal strain, but also by sex and estrus factors. The greater vulnerability to stress-ulcer and higher depression scores in WKY proestrus-estrus females provided data congruent with human clinical documentation[26].

Table 1. Summary (Means ± SEM) of Porsolt Forced-Swim Behaviors, and Stomach Ulcer Scores Following Desipramine Administration and Water-Restraint Stress

Treatments		Porsolt forced-swim behavior		Ulcer measures following water-restraint stress	
		Struggling(min)	Floating(min)	No. of Ulcers	Ulcer length(mm)
WKY	Placebo	1.12 ± 0.29	13.80 ± 0.34	16.60 ± 4.32	14.44 ± 2.55
	5 mg *	3.98 ± 1.43	10.10 ± 0.94	5.40 ± 0.24	4.60 ± 0.40
	10 mg	5.03 ± 2.17	8.92 ± 2.15	2.00 ± 0.80	1.14 ± 0.80
	20 mg	9.93 ± 1.48	3.99 ± 1.48	1.80 ± 2.08	0.74 ± 0.48
Wistar	Placebo	5.38 ± 1.39	8.56 ± 1.40	7.60 ± 2.16	4.76 ± 2.13
	5 mg	7.46 ± 0.40	6.48 ± 0.50	0.60 ± 0.40	0.20 ± 0.14
	10 mg	7.63 ± 1.19	6.27 ± 1.22	0	0
	20 mg	11.16 ± 0.50	3.28 ± 0.44	0	0
F-344	Placebo	5.58 ± 0.91	8.44 ± 0.91	8.20 ± 1.75	7.74 ± 1.44
	5 mg	5.86 ± 0.35	9.10 ± 0.36	0.20 ± 0.20	1.10 ± 0.20
	10 mg	6.84 ± 1.09	7.73 ± 1.09	0.60 ± 0.20	0.26 ± 0.26
	20 mg	10.13 ± 0.44	3.93 ± 0.45	.80 ± 0.49	0.32 ± 0.10

* Dose of desipramine in mg/kg body weight administered daily for nine days. Porsolt test was carried out on day seven.

These data strongly suggested that the stress response in WKY rats is characterized by a susceptibility to stress ulcer and the prevalence of depressive behavior. If this is the case, it is reasonable to assume that anti-depressant drugs would not only reduce depressive behavior, but also reduce the vulnerability to stress-ulcer. There are earlier reports which suggest this to be the case[27]. To test this hypothesis we exposed WKY, Wistar and F-344 rats to the anti-depressant,

desipramine (DMI), with either 5, 10, or 20 mg/kg/day for nine days. On day seven all rats were tested in the Porsolt forced swim test and on day nine all rats were exposed to water-restraint stress. DMI not only reduced depression in the forced swim test in a dose-dependent fashion, but also significantly reduced ulcer severity[28]. These data are summarized in Table 1.

If we apply the behavioral data for WKY rats to the diagnostic criteria for depression[19], a behavioral profile emerges suggesting the prevalence of depressive behavior in WKY rats (see Table 2). The behavioral data imply that WKY rats are emotionally very reactive to stress and this hyperreactivity is revealed by behavioral signs of depressive behavior.

Table 2. Application of Wistar Kyoto Rat Behaviors and Physiological Responses to DSM-III Criteria for Behavioral Depression

DSM-III Criteria	WYK Behaviors
. Diminished interest or pleasure	Hyponeophagia[20]
. Psychomotor retardation	Immobility in OFT and FST[8,16]
. Indecisiveness	Ambivalence in passive avoidance[17]
also:	
-brooding, obsessive rumination	Memory bias
-prevalence in female	Increase ulcer-depression in female WKY rats[25]
-reversal by anti-depressants	Desipramine reduces immobility[28]

PHYSIOLOGICAL RESPONSES

WKY rats reveal several behavioral responses of stress hyperreactivity, but a distinct physiological response pattern is also observable in these animals. In our earlier studies we reported that ulcerogenic stressors typically produced more ulcers in WKY rats as compared to other rat strains. This effect occurred consistently with either the ulcerogenic procedures of activity-stress[29], prone immobilization[15], or water-restraint stress[8]. In the majority of the behavioral studies reviewed in the previous section, animals were also exposed to the water-restraint ulcerogenic stressor. Table 3 summarizes the ulcer data from all these studies. In all instances WKY rats emerged as the most ulcer-vulnerable strain. Thus stress-ulcer is one of the characteristic physiological responses to stress in WKY rats.

The physiological system most likely involved in our WKY ulcer-depression syndrome is the hypothalamic-pituitary-adrenal (HPA) axis[30,31,32], and the HPA axis in WKY rats is hyperreactive to stress. This statement is based partly on the observation that the adrenocorticotropin (ACTH) response to stress in WKY rats is greater than the similar response in other rat strains. WKY and Wistar rats were surgically prepared with chronic jugular catheters and subsequently exposed to restraint stress. There were no differences in pre-stress basal plasma ACTH or corticosterone (CORT) values between strains. But, the ACTH stress response was significantly greater for WKY rats throughout the stress period. Surprisingly there were no strain differences in CORT. Thus, the exaggerated ACTH response of WKY

Table 3. Summary of Ulcer Data (Mean ±SEM) From Behavioral Studies Wherein Multiple Rat Strains Were Tested on Various Behavioral Test and Subsequently Exposed to the Water-Restraint Ulcerogenic Procedure

Behavioral Studies	Mean (± SEM) cumulative ulcer length-(mm).			
	WKY rats	Wistar rats	F-344 rats	SHR rats
Open field test (OFT) [33*]	85.0 ± 0.6	35.2 ± 5.4	---	60.6 ± 6.5
OFT [8]	13.5 ± 5.2	3.6 ± 1.8	6.8 ± 2.1	3.2 ± 0.9
OFT - gender differences[25]				
Male rats	27.3 ± 7.8	9.0 ± 2.4	11.2 ± 3.8	---
Female rats**	37.9 ± 4.9	13.5 ± 1.9	12.4 ± 2.3	---
Learned helplessness (LH)[8]	24.3 ± 3.8	3.2 ± 1.1	7.3 ± 1.6	27. ± 1.0
Forced swim test (FST)[8]	26.7 ± 6.1	2.9 ± 0.8	4.8 ± 1.7	4.9 ± 1.6
Elevated-plus maze[11]	20.8 ± 3.9	10.8 ± 2.2	16.3 ± 2.2	---
Defensive burying (DB)[11]	19.8 ± 2.3	10.1 ± 1.3	13.2 ± 1.0	---
Defensive withdrawal[11]	17.5 ± 1.8	13.6 ± 0.9	14.7 ± 1.6	---
Step-down passive avoidance[17]	20.8 ± 3.4	13.4 ± 1.7	15.6 ± 2.1	---
One-way passive avoidance[17]	25.4 ± 3.0	16.8 ± 2.8	15.9 ± 4.0	---
FST, OFT, LH, & DB[16]	13.7 ± 1.7	2.7 ± 0.3	---	---

* Ulcers induced by activity-stress procedure
** Tested during proestrus-estrus

rats occurred despite the presence of appropriate CORT levels. In addition, none of the rats from the comparison strain had ulcers, whereas all the WKY rats had ulcers[10].

The exaggerated ACTH response to stress in WKY rats could be attributed to either a pituitary hyperresponsiveness to corticotropin releasing factor (CRF), or a lack of sensitivity to the negative glucocorticoid feedback. One way to address this question involved simply removing the glucocorticoid negative feedback in the HPA-axis loop by adrenalectomy (ADX). Accordingly, WKY, Wistar or F-344 rats received either ADX, sham ADX, or ADX plus CORT replacement (in the form of CORT subdermal pellets), and these rats were exposed to the ulcerogenic water-restraint procedure. Intact WKY rats had dramatically more ulcers and higher anterior ACTH and proopiomelanocortin (POMC) mRNA levels than the other strains. ADX, in the WKY rats increased ulcer incidence, but had little effect on thymus weight, ACTH content or hypothalamic CRF mRNA levels in contrast to the profound, and opposite, effects of ADX on these parameters in the other strains. Furthermore, CORT replacement was without effect in WKY rats, while it reversed the effects of ADX in the other strains[34]. These data are summarized in Table 4. Thus, WKY rats that responded to stress with increased ulcers, already had enhanced synthesis of POMC mRNA. The mechanism underlying this dysregulation of the HPA-axis may be related to decreased efficacy of glucocorticoid negative feedback as manifested by diminished changes in response to ADX and CORT replacement. This glucocorticoid resistance in WKY rats resembles the relative insensitivity to glucocorticoid observed in individuals with endogenous depression[35]. Also, this proposed hyposensitivity of the corticotroph to the inhibitory action of glucocorticoid does not exclude the possibility that the dysregulation of the WKY HPA-axis may be attributable to an increased CRF secretion or an increased sensitivity of the corticotroph to CRF.

Table 4. Mean (± SEM) Ulcer, Thymus and HPA Measures in Adrenalectomized (ADX), Sham ADX, and Corticosterone Replacement (ADX+CORT) Groups Following Restraint Stress in WKY, Wistar and F-344 Rats

Treatment		Ulcer[1]	Thymus[2]	ACTH Content[3]	CRF mRNA[4]	POMC[5]
WKY	Sham	22.0 ± 2.7	104 ± 19	25.2 ± 1.5	1.12 ± .08	7.3 ± 3.2
	ADX	34.6 ± 3.4	110 ± 28	25.8 ± 1.3	1.18 ± .04	20.9 ± 6.3
	ADX+CORT	29.3 ± 4.2	96 ± 19	---	1.13 ± .03	11.2 ± 2.3
Wistar	Sham	11.7 ± 3.2	140 ± 15	18.6 ± 1.0	1.23 ± .10	2.5 ± 1.1
	ADX	1.7 ± 0.3	170 ± 47	26.2 ± 1.1	1.46 ± .27	11.5 ± 3.4
	ADX+CORT	10.6 ± 1.8	87 ± 16	---	1.00 ± .01	2.1 ± 0.4
F-344	Sham	12.3 ± 1.5	104 ± 19	20.9 ± 1.5	1.22 ± .01	2.9 ± 1.1
	ADX	2.2 ± 0.8	110 ± 28	24.4 ± 2.1	2.74 ± .16	10.3 ± 3.0
	ADX+CORT	13.7 ± 3.9	96 ± 19	---	1.33 ± .16	2.0 ± 0.3

[1] Mean cumulative ulcer length - mm.
[2] Thymus weight/body weight ratio - g/g x 1000
[3] ACTH - mg/anterior pituitary
[4] Relative CRF mRNA - CRF mRNA/β-actin mRNA ratio
[5] Relative POMC mRNA - POMC mRNA/β-actin mRNA ratio

DISCUSSION

There are significant differences in the biobehavioral stress response of WKY rats. To summarize, we have observed in the WKY rat: (a) high susceptibility to stress ulcer; (b) depressive behavior, (c) a high level of activity of the HPA axis in response to stress, and (d) a dysregulation of the HPA axis. These observations can form the basis of our hypothesis that WKY rats are endogenously hyperresponsive to stress. This hyperresponsiveness is manifested in a high susceptibility to stress ulcer as well as the hyperreactivity of the HPA axis. Since clinical studies have proposed a possible relationship between ulcer disease and depression[36,37,38], as well as between stressful events and depression[30,31,32], our original hypothesis can be further expanded. Thus, we believe that the WKY's hyperresponsiveness to stress leads to signs of behavioral depression, and this apparently strain-specific proclivity makes this rat strain a potential model of endogenous depression.

There are different kinds of animal models. Each model type emphasizes one aspect of the pathological condition that it represents. Thus, we have behavioral models that mimic the symptoms and signs of the human disorder, mechanistic models that emphasize the neurobiological mechanisms of the disorder, and empirical validity models that attempt to predict pharmacological outcome (for a critical review, see McKinney[39]). Rarely do we find all of these characteristics in the same animal model. Yet when we review the data from the WKY studies, we note that the WKY strain contains elements of the different model types. Thus the strain exhibits behaviors that mimic the behavioral disorder of depression. It reveals physiological processes (i.e., mechanisms) that have been reported in endogenous depression,

namely the insensitivity of the glucocorticoid system. Finally, anti-depressants reverse the alleged depressive behavior in WKY rats. The data reviewed in this paper, plus these theoretical considerations, would suggest that the WKY rat strain may indeed serve as a useful model of endogenous depression.

REFERENCES

1. H. Selye, Thymus and adrenals in the response of the organism to injuries and intoxications, *Brit J Exp Pathol.* 17:234 (1936).
2. H. Selye, The general-adaptation-syndrome and the diseases of adaptation, *in:* "Textbook of Endocrinology," Acta Endocrinologica, Inc., Montreal (1949).
3. K.A. Holyroyd, M.A. Appel, and F. Andrasik, *in:* "Stress reduction and prevention," D. Meichenbaum, M.E. Jaremko, eds., Plenum Press, New York (1983).
4. B.H. Natelson, Stress, predisposition and the onset of serious disease: Implications about psychosomatic etiology, *Neurosci Biobehav Rev.* 7:511 (1983).
5. M.J. Horowitz, Stress-response syndrome: Post-traumatic and adjustment disorders, *in:* "Psychiatry Vol 1", J.O. Cavenar, ed., Basic Books, New York (1986).
6. K. Okamoto, and K. Aoki, Development of a strain of spontaneously hypertensive rats, *Jpn Circ J.* 27:282 (1963).
7. W.P. Paré, Stress ulcer and open field behavior of spontaneously hypertensive, normotensive and Wistar rats, *Pavlovian J Biol Sci.* 24:54 (1989).
8. W.P. Paré, Stress ulcer susceptibility and depression in Wistar Kyoto (WKY) rats, *Physiol Behav.* 46:993 (1989).
9. P. Willner, Animal models of depression: An overview, *Pharmacol Ther.* 45:425 (1990).
10. W.P. Paré and E. Redei, Depressive behavior and stress ulcer in Wistar Kyoto rats, *J. Physiol (Paris).* 87:229 (1993).
11. W.P. Paré, The performance of WKY rats on three tests of emotional behavior, *Physiol Behav.* 51:1051 (1992).
12. L.K. Takahashi, N.H. Kalin, J.A. Vanden Burgt, and J.E. Sherman, Corticotropin-releasing factor modulates defensive-withdrawal and exploratory behavior in rats, *Behav Neurosci.* 103:648 (1989).
13. S. Pellows, P. Chopin, S.E. File, and M. Briley, Validation of open:closed arm entries in an elevated plus-maze as a measure of anxiety in the rat, *J Neurosci Meth.* 14:149 (1985).
14. J.P.J. Pinel, L.A. Symons, B.K. Christensen, and R.C. Tess, Development of defensive burying in Rattus norvegicus: Experience and defensive responses, *J Comp Psychol.* 103:359 (1989).
15. W.P. Paré, A comparison of two ulcerogenic techniques, *Physiol Behav.* 44:417 (1988).
16. W.P. Paré, Open field, learned helplessness, defensive burying and forced-swim tests in WKY rats, *Physiol Behav.* 55:433 (1994).
17. W.P. Paré, Passive-avoidance behavior in Wistar-Kyoto (WKY), Wistar, and Fischer-344 rats, *Physiol Behav.* 54:845 (1993).
18. T. Dalgleish, and F.N. Watts, Biases of attention and memory in disorders of anxiety and depression, *Clin Psychol Rev.* 10:589 (1990).
19. American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 3rd ed.-revised, Washington (1987).
20. W.P. Paré, Hyponeophagia in Wistar Kyoto (WKY) rats, *Physiol Behav.* in press (1994).
21. G.A. Kennett, S.L. Dickinson, and G. Curzon, Enhancement of some 5-HT-dependent behavioral responses following repeated immobilization in rats, *Brain Res.* 330:253 (1985).
22. W.P. Paré, Stress and consummatory behavior in the albino rat, *Psychol Rep.* 16:135 (1965).
23. B.P. Dohrenwend, and B.S. Dohrenwend, Sex differences and psychiatric disorders, *Am J Sociol.* 81:1447 (1976).
24. M.M. Weissman, and G.L. Klerman, Sex differences and the epidemiology of depression, *Arch Gen Psychiat.* 34:98 (1977).
25. W.P. Paré and E. Redei, Sex differences and stress response of WKY rats, *Physiol Behav.* 54:1179 (1993).
26. C. Ernst, and J. Angst, The Zurich study. XII, Sex and depression. Evidence from longitudinal epidemiological data, *Arch Psychiat Clin Neurol.* 241:222 (1992).

27. D.E. Hernandez, and B.G. Xue, Imipramine prevents stress gastric glandular lesions in rats, *Neurosci Lett.* 103:209 (1989).
28. W.P. Paré, Learning behavior, escape behavior, and depression in an ulcer susceptible rat strain, *Integrative Physiol Behav Sci.* 27:130 (1992).
29. W.P. Paré, The influence of food consumption and running activity on the activity-stress ulcer in the rat, *Am J Dig Dis.* 20:262 (1975).
30. H. Anisman, Vulnerability to depression: Contribution of stress, *in:* "Neurobiology of Mood Disorders," R.M. Post, J.C. Ballenger, eds., Williams and Wilkins, Baltimore (1984).
31. G.B. Glavin, Stress and brain noradrenaline: A review, *Neurosci & Biobehav Rev.* 9:233 (1985).
32. J.M. Weiss, and P.G. Simson, Neurochemical mechanisms underlying stress-induced depression, *in:* "Stress and Coping," T.M. Fields, P.M. McCabe, N. Schneiderman, eds., Lawrence Erlbaum Assoc., Hillsdale, NJ (1985).
33. W.P. Paré and G.T. Schimmel, Stress ulcer in normotensive and spontaneously hypertensive rats, *Physiol Behav.* 36:699 (1986).
34. E. Redei, W.P. Paré, F. Aird, and J. Kluczynski, Strain differences in hypothalamic-pituitary-adrenal activity and stress ulcer, *Am J Physiol.* 266:R353 (1994).
35. F. Holsboer, Implications of altered limbic-hypothalamic-pituitary-adrenocortical (LHPA) function for neurobiology of depression, *Acta Psychiat Scan Suppl.* 341:72 (1988).
36. J.H. McIntosh, R.W. Nasiry, D. McNeil, C. Coates, H. Mitchell, and D.W. Piper, Perception of life event stress in patients with chronic duodenal ulcer, *Scand J Gastroenterol.* 20:563 (1985).
37. J.H. Medalie, K.C. Stange, and S.J. Zyzanski, The importance of biopsychosocial factors in the development of duodental ulcer in a cohort of middle-aged men, *Am J Epidemiol.* 136:1280 (1992).
38. D.W. Piper, M. Grieg, J. Thomas, and J. Skinners, Personality patterns of patients with chronic gastric ulcer. Study of neuroticism and extroversion in a gastric ulcer and a control population, *Gastroenterology.* 73:444 (1977).
39. W.T. McKinney, Models of mental disorders, *in:* "A New Comparative Psychiatry", Plenum Press, New York (1988).